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Safety and Efficacy of Empiric De-escalation of Antibiotics for Pneumonia in the Intensive Care Unit

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Study Objectives

Primary objective:

- **Overall mortality during index hospitalization of patients in which broad-spectrum antibiotics were de-escalated vs. patients who received a full course**

Secondary objectives:

- **ICU length of stay (LOS) in days**
- **Hospital LOS in days**
- **Days dependent on mechanical ventilation**
- **Rate of readmission for infection within 30 days of discharge**
- **Rate of antibiotic re-escalation**
  - Defined as either a repeat course during index hospitalization or broadening of antibiotics

Research Background

- Pneumonia with risk factors (HAP/VAP) carries a 7-10% overall mortality
  - **Risk factors defined by the IDSA**
- Rapid de-escalation for resistant gram-positive organisms (Methicillin resistant *Staphylococcus aureus*) via nucleic acid amplification tests (MRSA NAAT)
  - **No test for gram-negative organisms**
- Each extra day of broad-spectrum antibiotics adds 4% chance of resistance
- Expectorated sputum and blood samples yield a pathogen 10% of the time in pneumonia

Giuliano *American Journal of Infection Control*. 2023;51(2):227-230. doi:10.1016/j.ajic.2022.06.016
Kalil *Clinical Infectious Diseases*. 2016;63(5):e61-e111. doi:10.1093/cid/ciw353
Teshome *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*. 2019;39(3):261-270. doi:10.1002/phar.2201
Corbo J imited usefulness of initial blood cultures in community acquired pneumonia. Emergency Medicine Journal.

Literature Background

Deshpande et al. (2021) reviewed admissions across 164 hospitals in the U.S. for culture negative pneumonia at 96 hours

- **Total N of 14,170 met criteria for de-escalation, were "clinically stable"**
- **1,924 patients de-escalated (13.6%)**
- **Slight difference in mortality. Decrease in ICU LOS and costs**

Khan et al. (2017) reviewed patients with pneumonia that had negative blood or sputum cultures at 96 hours

- **Compared to patients who were not de-escalated but clinically similar**
- **No difference in mortality observed**

Weiss et al. (2016) reviewed resistance rates following de-escalation of beta-lactams in ventilator associated pneumonia

- **No difference in mortality, disease relapse, or LOS**
- **De-escalation cohort: decrease in resistant gram-negative colonization**

Deshpande *Clinical Infectious Diseases*. 2020;72(8):1314-1322. doi:10.1093/cid/ciaa212
Khan *International Journal of Clinical Pharmacy*. 2017;39(4):906-912. doi:10.1007/s11096-017-0499-2
Weiss E *Intensive Care Medicine*. 2016;42(12):2098-2100. doi:10.1007/s00134-016-4448

Patient Criteria

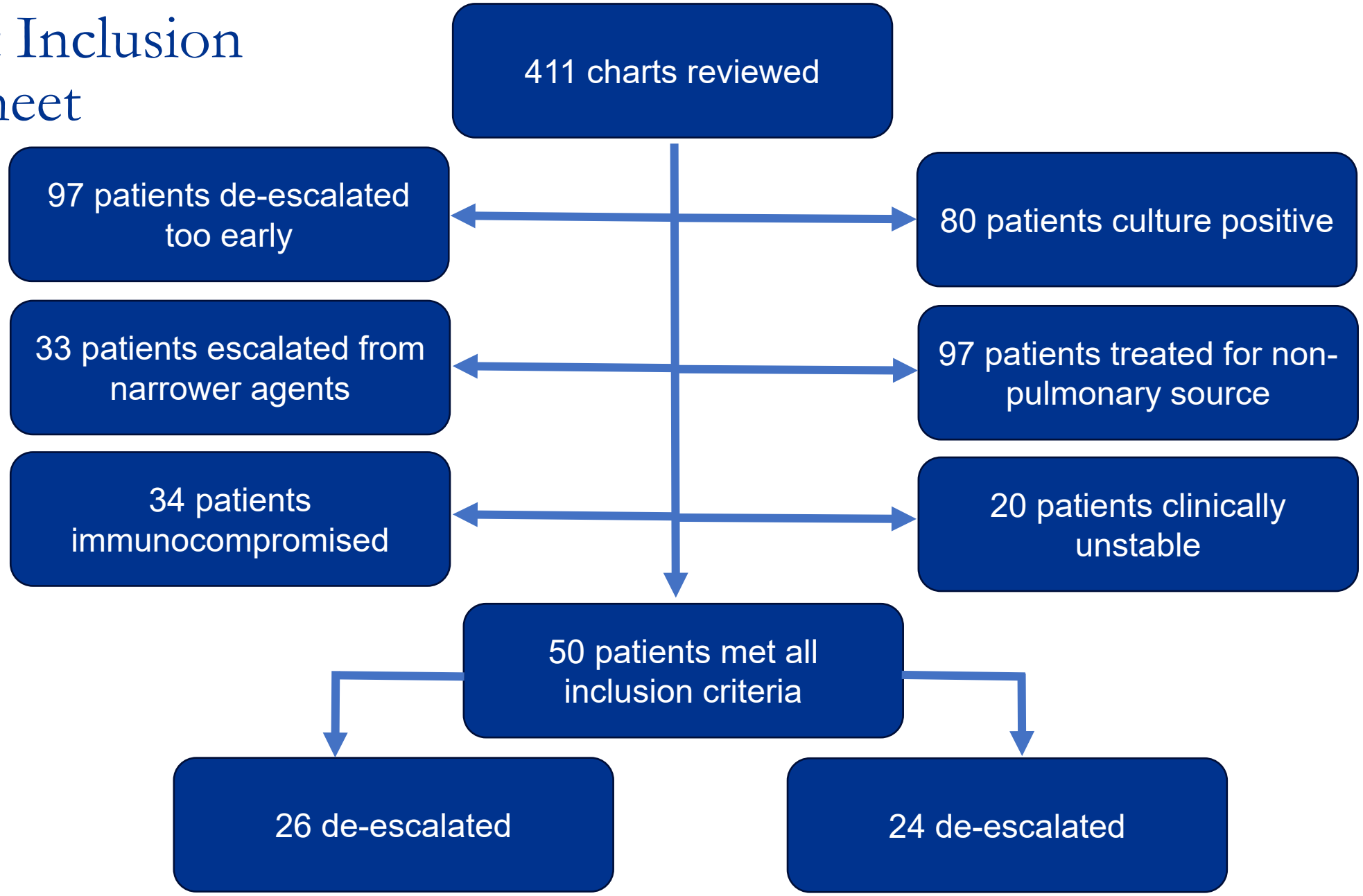
Inclusion criteria

- **Admitted to one of five included ICUs within the Swedish Health System**
- **≥ 18 years of age**
- **Received cefepime, ceftazidime, piperacillin-tazobactam, or meropenem for pneumonia for at least 72 hours**
- **Had a blood or sputum culture collected**

Exclusion criteria

- **Culture preliminary with a gram-negative organism**
- **Antibiotics for a non-pulmonary source**
- **Confirmed resistant gram-negative infection within the past 90 days**
- **Immunocompromised or absolute neutrophil count below 1,500**
- **Broad spectrum antibiotics because of treatment failure with narrower agents**
- **Clinically unstable***

Patient Inclusion Flowsheet



Results – Baseline Characteristics

Characteristic	De-escalated (26)	Not De-escalated (24)	P value
Age	65 (±15.1)	77.6 (±12.3)	**0.03**
Gender (male)	16 (62%)	15 (63%)	0.9
APACHE II	18 (±7.5)	17.5 (±9)	0.39
History COPD, CHF, ESRD	42%	33%	0.74
Acute renal failure	23%	37.5%	0.13
Initial antibiotic (cefepime)	88.5%	75%	0.89
Mechanical Ventilation	38.5%	37.5%	0.94

Results - Outcomes

Primary outcome – Mortality during index admission

De-escalated	Not de-escalated	Risk Ratio (95% CI)	P value
7.7% (2/26)	33% (8/24)	**0.23 (0.054-0.98)**	**0.047**

Secondary outcomes, excluding one statistical outlier (averages reported first ±STD, then median with IQR)

Outcome	De-escalated	Not De-escalated	P value	RR (95% CI)
ICU LOS	6.2(±3.2) 6 (4)	7.1 (±3.1) 6 (4.5)	0.35	N/A
Hospital LOS	8.6 (±5.3) 8 (9)	9.4 (±5) 7.5 (6)	0.66	N/A
Days on vent	3.6(±3.7) 2 (4.5)	4.7 (±3) 5 (5)	0.49	N/A
Re-escalation	7.7% (2/26)	4.2% (1/24)	0.61	1.85 (0.18-19.1)
Re-admission	12.5% (3/24)	13.3% (2/16)	0.94	0.94 (0.18-4.97)

Discussion

Study strengths:

- **Primary outcome in de-escalated group met the expected outcome on a population level**
- **Groups statistically similar at baseline**

Study weaknesses:

- **Retrospective chart review**
- **Non-de-escalated group saw a much higher mortality**
  - They all met criteria for de-escalation, would more have died if de-escalated?
- **Both groups had similar admission rates to specialty ICUs, higher acuity does not explain higher mortality rate**

Conclusion

In this small, single-center, multi-campus study, empiric de-escalation of broad-spectrum antibiotics was not associated with an increased risk of mortality

There were no differences observed in rates of re-escalation or re-admission between either group

Overall ICU, hospital, and ventilator days were similar among both groups

- **When excluding one outlier in de-escalated group, trend for values to favor de-escalation**

De-escalation at 72 hours in culture negative pneumonia for clinically stable patients appears to be a safe and effective method of antimicrobial stewardship

References

1. Deshpande *Clinical Infectious Diseases*. 2020;72(8):1314-1322. doi:10.1093/cid/ciaa212
2. Khan *International Journal of Clinical Pharmacy*. 2017;39(4):906-912. doi:10.1007/s11096-017-0499-2
3. Weiss E *Intensive Care Medicine*. 2016;42(12):2098-2100. doi:10.1007/s00134-016-4448
4. Giuliano *American Journal of Infection Control*. 2023;51(2):227-230. doi:10.1016/j.ajic.2022.06.016
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7. Corbo J imited usefulness of initial blood cultures in community acquired pneumonia. Emergency Medicine Journal.

Thank you!
Questions
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